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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,390	12/17/2001	Manuel Vega	37851-912	5547

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,390	VEGA ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,46,62,70,94 and 95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,46,62,70,94 and 95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/19/05,12/30/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of an amendment filed 1/5/06. Claims 45 and 62 were amended. Currently claims 45, 46, 62, 70, 78, 94, and 95 are pending and under examination with respect to SEQ ID NO: 113, as elected.

Election/Restrictions

2. Applicant again argues the restriction requirement. The requirement has been made final. In any event, as the claims have not been found to be allowable, further analysis of the species in claim 62 has been undertaken. Upon resolution of the rejections of record further analysis of the claims regarding the non-elected species will take place as is appropriate. The remainder of the arguments regarding the restriction requirement has been previously addressed, and will not be considered further as the requirement has been made final.

3. This application contains claims drawn to an invention nonelected with traverse in the response filed 7/6/04 and 12/23/04. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

5. The disclosure is objected to because of the following informalities: page 17, line 30 identifies a series of amino acids as "hydrophobic" yet the majority of the amino acids identified are clearly recognized in the art as hydrophilic. This then is clearly repugnant to the art. It is also noted that the Genbank accession numbers referring to the different serotypes of AAV, such as in the paragraph starting at line 3 of page 9 are not in a searchable format. If the accession numbers as listed are searched, no results are returned. Therefore, the appropriately searchable accession numbers are required. Thus changing "NC001729" to --NC_001729--, for example, would be remedial.

Appropriate correction is required.

Claim Objections

6. Claim 62 is objected to because of the following informalities: the amendment has attempted to correct the lack of sequence compliance in this claim, yet the SEQ ID NOs entered do not correspond to the proteins bearing the mutations claimed. Rather the newly entered SEQ ID NOs the wild-type protein, not reflecting the changes that are claimed. For example residue 350 of SEQ ID NO: 747 is indeed a T not an N as claimed. It appears that the appropriate SEQ ID NOs are listed in the Table spanning pages 53-71 of the specification. Applicant should amend claim 62 to refer to the appropriate SEQ ID NO that reflects the mutant amino acid sequence. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 45, 62, 70, 78, 94, and 95are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection necessitated by the amendment to the claims.

9. Claim 62 recites "residue 1 corresponds to residue 1 of Rep78 protein encoded by nucleotides 321-323 SEQ ID No. 746) of the AAV-2 genome". First, there is an unmatched parenthesis after "746". This must be corrected. Second, the language here could easily confuse the skilled artisan with regard to the true start. Upon inspection of SEQ ID NO: 746 in the sequence listing, it is apparent that the coding sequence starts at residues 321-323 of SEQ ID NO: 746, while SEQ ID NO: 746 begins at nucleotide 321 of the AAV-2 genome. As written the claim suggests that SEQ ID NO: 746 is the entire AAV-2 genome, while this is clearly not the case. Due to this confusion, the skilled artisan would be unable to ascertain the metes and bounds of this limitation in the claim.

Claim Rejections - 35 USC § 112-1

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 45, 46, 62, 70, 78, 94, and 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled

in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are being examined with respect to the elected species of a T to N mutation at position 350, represented by SEQ ID NO: 113. Thus, the claims are drawn to a nucleic acid molecule which encodes a mutant Rep protein, where the mutation is a T to N mutation at position 350, where the reference point is residue 1 of Rep 78 in AAV-2. The claims are thus drawn to a nucleic acid encoding any mutant Rep protein comprising the equivalent mutation including Rep 78, Rep 68, Rep 52,and Rep 40 from any of the AAV serotypes, including AAV-1, AAV-2, AAV-3, AAV-3b, AAV-4, AAV-5, or AAV-6. The claim are additionally drawn to cells comprising the nucleic acid, recombinant AAV vectors comprising the nucleic acid, and cells comprising the recombinant AAV vector.

12. The specification discloses a method whereby the Rep proteins of AAV-2 undergo a process of directed evolution in a screen to identify mutants that result in alterations in the viral titer. "To identify candidate amino acid (aa) positions on the rep protein involved in rep protein activity an Ala-scan as performed on the rep sequence [from AAV-2]. For this, each amino acid in the rep protein was replaced with Alanine" (page 45, lines 3-6). As was the case with all of the alanine mutations, the mutation of T to A at position 350 resulted in a decrease in viral production. There is then a table that shows that position 350 in AAV-2 corresponds to position 350 in AAV-1, AAV-3, AV-3b, AAV-4, and AAV-6 and position 346 in AAV-5. "The rep proteins encoded by these sets of nucleic acid molecules were those in which each amino acid position identified as a "hit" in the ala-scan step [including 350], were each sequentially replaced by all remaining 18 amino acids using site directed mutagenesis" (page 52, lines4-8). These mutants were then screened for an increase in AAV production. Among the "leads" identified

was the replacement of T by N at position 350. Thus again, sufficient description exists for a T to N mutation in AAV-2, as this is what was exemplified.

13. The question then arises, is possession of this species sufficient to convince the skilled artisan that the inventors were in possession of the fully claimed genus? In short, no, this would not signify to the skilled artisan possession of the entire genus claimed. Indeed, the specification itself teaches that the mutations identified would not necessarily correlate to mutations in all forms of the rep protein or to the rep proteins of all serotypes of AAV.

14. Referring to Figure 3A, position 350 of AAV-2 is indeed a T residue. In five of the other six serotypes, this position is occupied by an A. Thus, how could the skilled artisan assume that an A to N mutation in any of these serotypes would have the same activity as the exemplified T to N mutation? There is no assurance that these mutations would have the same type of activity. The mutations identified in the instant application to AAV-2 rep are completely random and bear no reasoning for mutating the particular residues. Thus no structure function relationship exists between the identified mutations and the protein. In essence there is no apparent understanding why, for example the T to N mutation that is exemplified has the effect that it does.

15. If indeed this residue is so critical for viral titer, why then is it not conserved among the different serotypes? Additionally the method that led to the initial identification of position 350 was an alanine scanning method. There is no way this method could have identified position 350 is any of the five other serotypes had been used in this screen. As Figure 3A shows, this position is already an alanine in these other serotypes. If indeed this position were so critical, then wild type AAV-1, AAV-3, AAV-3b, AAV-4, and AAV-6 would necessarily have reduced viral titer relative to AAV-2 or AAV-5, as the initial screen to identify "hits" showed that a T to A

mutation at position 350 in AAV-2 resulted in a reduced viral titer. The specification does not teach this and there is no fair suggestion of this difference in the prior art. The skilled artisan would have no reason to believe that the mutation to N at position 350 in AAV-2 would correlate to a mutation to N at position 350 or 346 in any other AAV serotype. Thus, the skilled artisan would find no evidence, based on the specification, as filed, that the inventors were in possession of the full genus of a mutation at position 350 to N in any AAV-serotype.

16. This then leads to the question; does this mutation in the full-length rep protein, Rep 78 of AAV-2 suggest to the skilled artisan that the inventors were in possession of all of the species of rep, including Rep 68, Rep 52, and Rep 40? Again, the short answer is no. It is understood that the different rep proteins of AAV-2 would possess the same T residue at this position, as the differences between the rep proteins are due to differential promoter use and differential splicing, yet all four proteins use the same reading frame. It is further understood that a T to N mutation in Rep 78 would necessarily lead to a T to N mutation is the other three rep proteins. The question then becomes, would each of the individual rep proteins be expected to individually lead to an increase in viral titer? "Rep 52 and 40, the two minor forms of the Rep proteins, do not bind to ITRs and are dispensable for viral DNA replication and site-specific integration" (page 3, line7-9). As Rep 52 and Rep 40 apparently play no role in ITR binding, viral replication, or viral integration, the skilled artisan would have no reason to conclude, absent evidence to the contrary, that a mutant form of Rep 52 or Rep 40 would be capable of leading to an increased viral titer. Again, there is no teaching in the specification and no finding in the prior art that would suggest that Rep 52 or Rep 40 would have the activity that leads to the increased viral titer seen in the T

to N mutation at position 350 of Rep 78. Thus, the skilled artisan would not have reason to believe the inventors were in possession of the invention as broadly claimed.

Response to Arguments

17. Applicant's arguments filed 1/5/06 have been fully considered but they are not persuasive. Applicant has argued against the propriety of the rejection under the written description requirement of 35 U.S.C. 112, first paragraph, through a variety of avenues that various pieces of case law suggest about the requirements under 112, first paragraph regarding written description. None of these arguments are relevant to the rejection of record however. The rejection specifically points out, through analysis of the sequences why the skilled artisan would not be of the opinion that the claimed mutation, T to N at position 350, would result in the same phenotypes in different AAV serotypes. This analysis has in no way been addressed. As such the rejection is maintained.

18. Claims 45, 46, 62, 70, 78, 94, and 95 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a mutant form of Rep 78 or Rep 68 of AAV-2 (SEQ ID NO: 113), a cell comprising this nucleic acid, recombinant AAV-2 comprising this nucleic acid, and a cell comprising this recombinant AAV-2, does not reasonably provide enablement for a nucleic acid encoding an equivalent mutation in other AAV serotypes, Rep 52 or Rep 40 comprising this mutation, cells containing this nucleic, recombinant AAV comprising this nucleic acid, or cells comprising this recombinant AAV. The specification

does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

19. When considering whether the specification in view of the prior art enables the skilled artisan to practice the claimed invention without undue levels of experimentation a number of factors are considered in making this determination as delineated by In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

20. As delineated above, there is no teaching in the specification and no suggestion in the art that a mutation at position 350 to N would necessarily function in the same regard as the T to N mutation exemplified in Rep 78 of AAV-2. The claims are broadly drawn as they encompass any of the versions of the rep protein derived from any of the AAV serotypes. The variation in the residue at position 350, and the apparently unknown function of Rep 52 and Rep 40 means that there is high degree of unpredictability in this regard. The specification exemplifies a T to N or at position 350 in Rep 78 of AAV-2. As argued above, there is no evidence that this would correlate to similar mutations in other serotypes. The specification makes no mention of the sequence differences at position 350 between the different serotypes, except for the alignment in Figure 3. There is no evidence of record that REP proteins from other serotypes bearing a mutation where the equivalent residue of 350 is mutated to N, would have a similar effect on viral titer. Thus to make any other serotype bearing a residue 350 to N mutation would require an

undue level of experimentation. There is a high likelihood that no other serotype would result in the same phenotype as AAV-2, for the reasons delineated above and as such to make an AAV vector comprising this mutation in other serotypes would require the skilled artisan to identify other sites in a trial and error fashion. This constitutes an undue level of experimentation.

Response to Arguments

21. Applicant's arguments filed 1/5/06 have been fully considered but they are not persuasive. As above, the majority of Applicant's arguments in no way addresses the merits of the rejection of record, and as such is irrelevant.

22. It is acknowledged that page 19 of the 1/5/06 amendment does indeed address certain points of the rejection. First, the second full paragraph of page 19 alleges that Figure 3 does not show an alignment. Contrary to this page 5, line 25 of the specification states, "FIGURES 3A and 38 show the alignment of amino acid sequences of Rep78". Indeed, however, Applicant supports Examiner's position that it would seem highly unlikely that a position 350 to N mutation the other serotypes aside from the exemplified AAV-2 would result in an alteration in titer. The rejection clearly states that due the lack of any difference in titer among different serotypes one would not have identified position 350 by alanine scanning. With no difference in titer it calls into question the whether this position plays a critical role in viral titer.

23. In the next paragraph Applicant states that because the Rep proteins share coding sequence it is improper to consider them individually. This is incorrect, as despite the fact that the different forms of the Rep protein do indeed share the same reading frame, the fact the claims are treating the different Rep protein individually means the rejection must address the individual

proteins. As presently drawn the claims are drawn to individual Rep proteins. It is well within the level of ordinary skill in the art to express only a single form of the Rep proteins. The claims encompass this possibility. The rejection addresses the fact that there is no reason to believe that either of Rep52 or Rep40 alone would lead to the effects on viral titer if expressed individually in the context of an infection, for example through exogenous expression form a plasmid. It is for this reasons that the rejection is made specifically pointing out the apparent inability of Rep52 or Rep40 to result in the desired phenotype of an increase titer.

24. Applicant's arguments, see the section bridging pages 21 and 22 of the amendment, filed 1/5/06, with respect to the utility rejection have been fully considered and are persuasive. Since the claims specifically refer to mutant virus, in the context of the specification, this indicates manipulation. The rejection of the claims under 35 U.S.C. 101 has been withdrawn.

Conclusion

25. No claim is allowed.

26. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

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